

Search Plan and Results

Question

What effect does folic acid supplementation (with or without additional B vitamin supplementation) have on risk of CVD among persons with or without pre-existing vascular disease? (DGAC 2010)

Date Searched

1) 2/09/09, 2) 2/20/09, 3)7-21-09

Inclusion Criteria

Subjects/Population: Human subjects.

Age: Children, men and women of all ages.

Setting: International.

Health Status: Healthy and those with elevated chronic disease risk (CHD/CVD, Type 2 diabetes, metabolic syndrome and obesity).

Nutrition Related Problem/Condition: None.

Search Criteria

Study Design Preferences: RCT or clinical controlled studies, large non-randomized observational studies, cohort, case-control studies, systematic reviews and meta-analysis.

Size of Study Groups: The sample size must equal 10 adults for each study group. For example, this would include 10 patients in the intervention group and 10 patients in the control or comparison group.

Study Drop Out Rate: Less than 20%; preference for smaller dropout rates.

Year Range: May 2004 to July 2009.

Authorship: If an author is included on more than one review article or primary research article that is similar in content, the most recent review or article will be accepted and earlier versions will be rejected.

Languages: Limited to articles in English.

Other: Article must be published in peer-reviewed journal.

Exclusion Criteria

Subjects/Population

- Animal and in vitro studies
- Malnourished/third-world populations or disease incidence not relative to US population (e.g., malaria).

Age: Not applicable.

Setting: Hospitalized patients.

Health Status: Medical treatment/therapy and diseased subjects (already diagnosed with disease related to study purpose).

Nutrition Related Problem/Condition: All conditions.

Search Criteria

Study Design Preferences: Not applicable.

Size of Study Groups: Sample sizes <10.

Study Drop Out Rate: If the dropout rate in a study is 20% or greater, the study will be rejected.

Year Range: Prior to May 2004.

Authorship: Studies by same author similar in content.

Languages: Articles not in English.

Other: Abstracts or presentations and articles not peer reviewed (websites, magazine articles, Federal reports, etc.).

Search Terms: Search Vocabulary

Comparators

- Intake levels/consumption levels
- Fortification
- Supplementation.

Health outcomes/clinical disease: CVD (morbidity and mortality)

Other terms: NHANES.

Electronic Databases

("Folic Acid"[Mesh] OR "folate"[All Fields]) AND ("Food, Fortified"[Mesh] OR "Dietary Supplements"[Mesh] OR diet[Mesh] OR intake[All Fields]) AND "english and humans"[Filter] AND "cardiovascular diseases"[MeSH Terms] ("Folic Acid"[Mesh] OR "folate"[All Fields]) AND "english and humans"[Filter] AND "cardiovascular diseases"[MeSH Terms] AND meta ("Folic Acid"[Mesh] OR "folate"[All Fields]) AND "english and humans"[Filter] AND "cardiovascular diseases"[MeSH Terms] Limits: Meta-Analysis ("Folic Acid" OR "folate"[All Fields]) AND (supplement* OR "Dietary Supplements"[Mesh]) AND (stroke[mh] OR "Vascular Diseases"[mh]) AND "cardiovascular diseases"[MeSH Terms]

Total hits from all electronic database searches: 741

Total articles identified to review from electronic databases: 63

Articles Identified Via Handsearch or Other Means

Hand search articles: 1

Summary of Articles Identified to Review

Number of Primary Articles Identified: 4

Number of Review Articles Identified: 1

Total Number of Articles Identified: 5

Number of Articles Reviewed but Excluded: 59

List of Articles Included for Evidence Analysis

Meta-analysis

Bazzano LA, Reynolds K, Holder KN, He J. Effect of folic acid supplementation on risk of cardiovascular diseases: A meta-analysis of randomized controlled trials.

www.ncbi.nlm.nih.gov/pubmed/17164458 *JAMA*. 2006 Dec 13; 296 (22): 2, 720-2, 726. Erratum in: *JAMA*. 2007 Mar 7; 297 (9): 952. PMID: 17164458.

Primary Articles

Albert CM, Cook NR, Gaziano JM, Zaharris E, MacFadyen J, Danielson E, Buring JE, Manson JE. Effect of folic acid and B vitamins on risk of cardiovascular events and total mortality among women at high risk for cardiovascular disease: A randomized trial. www.ncbi.nlm.nih.gov/pubmed/18460663 *JAMA*. 2008 May 7; 299 (17): 2, 027-2, 036. PMID: 18460663.

Bønaa KH, Njølstad I, Ueland PM, Schirmer H, Tverdal A, Steigen T, Wang H, Nordrehaug JE, Arnesen E, Rasmussen K; NORVIT Trial Investigators. [Homocysteine lowering and cardiovascular events after acute myocardial infarction](#). *N Engl J Med*. 2006 Apr 13; 354 (15): 1, 578-1, 588. Epub 2006 Mar 12. (Hand search) PMID: 16531614.

Ebbing M, Bleie Ø, Ueland PM, Nordrehaug JE, Nilsen DW, Vollset SE, Refsum H, Pedersen EK, Nygård O. [Mortality and cardiovascular events in patients treated with homocysteine-lowering B vitamins after coronary angiography: A randomized controlled](#)

[trial](#). *JAMA*. 2008 Aug 20; 300(7): 795-804. PMID: 18714059 (HS).

Ray JG, Kearon C, Yi Q, Sheridan P, Lonn E; Heart Outcomes Prevention Evaluation 2 (HOPE-2) Investigators. [Homocysteine-lowering therapy and risk for venous thromboembolism: A randomized trial](#). *Ann Intern Med*. 2007 Jun 5; 146 (11): 761-767. Epub 2007 Apr 30. PMID: 17470822.

List of Excluded Articles with Reason

Excluded Articles	Reason for Exclusion
Antoniades C, Antonopoulos AS, Tousoulis D, Marinou K, Stefanadis C. Homocysteine and coronary atherosclerosis: From folate fortification to the recent clinical trials. www.ncbi.nlm.nih.gov/pubmed/19029125 <i>Eur Heart J</i> . 2009 Jan; 30 (1): 6-15. Epub 2008 Nov 23. Review. PMID: 19029125.	It does not answer the question. About Hcy and CVD.
Bleys J, Miller ER 3rd, Pastor-Barriuso R, Appel LJ, Guallar E. Vitamin-mineral supplementation and the progression of atherosclerosis: A meta-analysis of randomized controlled trials. www.ncbi.nlm.nih.gov/pubmed/17023716 <i>Am J Clin Nutr</i> . 2006 Oct; 84 (4): 880-887; quiz 954-955. PMID: 17023716.	It does not answer the question. About antioxidants and B vitamins.
Boston AG, Jacques PF, Liaugaudas G, Rogers G, Rosenberg IH, Selhub J. Total homocysteine lowering treatment among coronary artery disease patients in the era of folic acid-fortified cereal grain flour. www.ncbi.nlm.nih.gov/pubmed/11884295 <i>Arterioscler Thromb Vasc Biol</i> . 2002 Mar 1; 22 (3): 488-491. PMID: 11884295.	It does not answer the question. About homocysteine.
Carlsson CM. Homocysteine lowering with folic acid and vitamin B supplements: Effects on cardiovascular disease in older adults. www.ncbi.nlm.nih.gov/pubmed/16872232 <i>Drugs Aging</i> . 2006; 23 (6): 491-502. Review. PMID: 16872232.	It does not answer the question. About B supplements and cardiovascular protection.
Clarke R, Collins R. Can dietary supplements with folic acid or vitamin B6 reduce cardiovascular risk? Design of clinical trials to test the homocysteine hypothesis of vascular disease. www.ncbi.nlm.nih.gov/pubmed/9919473 <i>J Cardiovasc Risk</i> . 1998 Aug; 5 (4): 249-255. No abstract available. PMID: 9919473.	Not a systematic review.

<p>De Bree A, Mennen LI, Hercberg S, Galan P. Evidence for a protective (synergistic?) effect of B-vitamins and omega-3 fatty acids on cardiovascular diseases. www.ncbi.nlm.nih.gov/pubmed/15116076 <i>Eur J Clin Nutr.</i> 2004 May; 58 (5): 732-744. PMID: 15116076.</p>	<p>It does not answer the question.</p>
<p>Goh YI, Bollano E, Einarson TR, Koren G. Prenatal multivitamin supplementation and rates of congenital anomalies: A meta-analysis. www.ncbi.nlm.nih.gov/pubmed/17022907 <i>J Obstet Gynaecol Can.</i> 2006 Aug; 28 (8): 680-689. Review. PMID: 17022907.</p>	<p>It does not answer the question. Folic acid intake is not quantify in this article.</p>
<p>Kang JH, Cook N, Manson J, Buring JE, Albert CM, Grodstein F. A trial of B vitamins and cognitive function among women at high risk of cardiovascular disease. www.ncbi.nlm.nih.gov/pubmed/19064521 <i>Am J Clin Nutr.</i> 2008 Dec; 88 (6): 1, 602-1, 610. PMID: 19064521.</p>	<p>It does not answer the question. About cognitive function.</p>
<p>Klerk M, Durga J, Schouten EG, Kluft C, Kok FJ, Verhoef P. No effect of folic acid supplementation in the course of one year on haemostasis markers and C-reactive protein in older adults. www.ncbi.nlm.nih.gov/pubmed/16113791 <i>Thromb Haemost.</i> 2005 Jul; 94 (1): 96-100. PMID: 16113791.</p>	<p>It does not answer the question. About supplementation and homocysteine.</p>
<p>Lewis SJ, Ebrahim S, Davey Smith G. Meta-analysis of MTHFR 677C->T polymorphism and coronary heart disease: Does totality of evidence support causal role for homocysteine and preventive potential of folate? www.ncbi.nlm.nih.gov/pubmed/16216822 <i>BMJ.</i> 2005 Nov 5;331 (7524): 1, 053. Epub 2005 Oct 10. Review. PMID: 16216822.</p>	<p>It does not answer the question. About genotype. Not a systematic review.</p>
<p>Malinow MR, Duell PB, Irvin-Jones A, Upson BM, Graf EE. Increased plasma homocyst(e)ine after withdrawal of ready-to-eat breakfast cereal from the diet: Prevention by breakfast cereal providing 200 microg folic acid. www.ncbi.nlm.nih.gov/pubmed/10963464 <i>J Am Coll Nutr.</i> 2000 Aug; 19 (4): 452-457. PMID: 10963464.</p>	<p>It does not answer the question. About homocysteine.</p>
<p>McCully KS. Homocysteine, vitamins and vascular disease prevention. www.ncbi.nlm.nih.gov/pubmed/17991676 <i>Am J Clin Nutr.</i> 2007 Nov; 86 (5): 1, 563S-1, 568S. Review. PMID: 17991676.</p>	<p>It does not answer the question. About homocysteine.</p>
<p>McEligot AJ, Rock CL, Gilpin EA, Pierce JP. Responsiveness of homocysteine concentrations to food and supplemental folate intakes in smokers and never-smokers enrolled in a diet intervention trial. www.ncbi.nlm.nih.gov/pubmed/16497600 <i>Nicotine Tob Res.</i> 2006 Feb; 8 (1): 57-66. PMID: 16497600.</p>	<p>It does not answer the question. About homocysteine.</p>

<p>McKay DL, Perrone G, Rasmussen H, Dallal G, Blumberg JB. Multivitamin/mineral supplementation improves plasma B-vitamin status and homocysteine concentration in healthy older adults consuming a folate-fortified diet. www.ncbi.nlm.nih.gov/pubmed/11110875.</p>	<p>It does not answer the question. About supplementation and homocysteine.</p>
<p>Moats C, Rimm EB. Vitamin intake and risk of coronary disease: Observation vs. intervention. <i>Curr Atheroscler Rep.</i> 2007 Dec; 9 (6): 508-514. Review. www.ncbi.nlm.nih.gov/pubmed/18377792 PMID: 18377792.</p>	<p>*Not a systematic review. It doesn't answer the question.</p>
<p>Muskiet FA. The importance of (early) folate status to primary and secondary coronary artery disease prevention. www.ncbi.nlm.nih.gov/pubmed/15964170 <i>Reprod Toxicol.</i> 2005 Sep-Oct; 20 (3): 403-410. Review. PMID: 15964170.</p>	<p>*Not a systematic review.</p>
<p>Ntaios GC, Savopoulos CG, Chatzinikolaou AC, Kaiafa GD, Hatzitolios A. Vitamins and stroke: The homocysteine hypothesis still in doubt. <i>Neurologist.</i> 2008 Jan; 14 (1): 2-4. Review. www.ncbi.nlm.nih.gov/pubmed/18195649 PMID: 18195649.</p>	<p>It does not answer the question. Not a systematic review. About vitamins and CVD.</p>
<p>Quinlivan EP, McPartlin J, McNulty H, Ward M, Strain JJ, Weir DG, Scott JM. Importance of both folic acid and vitamin B12 in reduction of risk of vascular disease. <i>Lancet.</i> 2002 Jan 19; 359(9302): 227-228. PMID: 11812560.</p>	<p>It does not answer the question. About homocysteine.</p>
<p>Rydlewicz A, Simpson JA, Taylor RJ, Bond CM, Golden MH. The effect of folic acid supplementation on plasma homocysteine in an elderly population. <i>QJM.</i> 2002 Jan; 95 (1): 27-35. PMID: 11834770.</p>	<p>It does not answer the question. About supplementation and homocysteine.</p>
<p>Sauer J, Mason JB, Choi SW. Too much folate: A risk factor for cancer and cardiovascular disease? www.ncbi.nlm.nih.gov/pubmed/19057184 <i>Curr Opin Clin Nutr Metab Care.</i> 2009 Jan; 12 (1): 30-36. Review. PMID: 19057184.</p>	<p>* Not a systematic review.</p>
<p>Smolková B, Dusinská M, Raslová K, Barancoková M, Kazimírová A, Horská A, Spustová V, Collins A. Folate levels determine effect of antioxidant supplementation on micronuclei in subjects with cardiovascular risk. <i>Mutagenesis.</i> 2004 Nov; 19 (6): 469-476. PMID: 15548759.</p>	<p>It does not answer the question. About antioxidants.</p>
<p>Tucker KL, Olson B, Bakun P, Dallal GE, Selhub J, Rosenberg IH. Breakfast cereal fortified with folic acid, vitamin B-6, and vitamin B-12 increases vitamin concentrations and reduces homocysteine concentrations: a randomized trial. <i>Am J Clin Nutr.</i> 2004 May; 79 (5): 805-811. PMID: 15113718.</p>	<p>It does not answer the question. About supplementation and homocysteine.</p>

<p>Van Beynum IM, den Heijer M, Blom HJ, Kapusta L. The MTHFR 677C->T polymorphism and the risk of congenital heart defects: A literature review and meta-analysis. www.ncbi.nlm.nih.gov/pubmed/17965089 <i>QJM</i>. 2007 Dec; 100 (12): 743-753. Epub 2007 Oct 26. Review. PMID: 17965089.</p>	<p>It does not answer the question.</p>
<p>Villa P, Perri C, Suriano R, Cucinelli F, Panunzi S, Ranieri M, Mele C, Lanzone A. L-folic acid supplementation in healthy postmenopausal women: Effect on homocysteine and glycolipid metabolism. <i>J Clin Endocrinol Metab</i>. 2005 Aug; 90 (8): 4, 622-4, 629. Epub 2005 May 17. PMID: 15899950.</p>	<p>It does not answer the question. About homocysteine.</p>
<p>Villa P, Suriano R, Costantini B, Macrì F, Ricciardi L, Campagna G, Lanzone A. Hyperhomocysteinemia and cardiovascular risk in postmenopausal women: The role of Folate supplementation. www.ncbi.nlm.nih.gov/pubmed/17311496 <i>Clin Chem Lab Med</i>. 2007; 45 (2): 130-135. Review. PMID: 17311496.</p>	<p>It does not answer the question.</p>
<p>Wald DS, Bishop L, Wald NJ, Law M, Hennessy E, Weir D, McPartlin J, Scott J. Randomized trial of folic acid supplementation and serum homocysteine levels. <i>Arch Intern Med</i>. 2001 Mar 12; 161 (5): 695-700. PMID: 11231701.</p>	<p>It does not answer the question. About supplementation and homocysteine.</p>
<p>Wenger NK. Do diet, folic acid, and vitamins matter? What did we learn from the Women's Health Initiative, the Women's Health Study, the Women's Antioxidant and Folic Acid Cardiovascular Study, and other clinical trials? www.ncbi.nlm.nih.gov/pubmed/18090063 <i>Cardiol Rev</i>. 2007 Nov-Dec; 15 (6): 288-290. Review. PMID: 18090063.</p>	<p>Monograph.</p>

Excluded Articles (July 21-09)	Reason for Exclusion
<p>Andersson A, Jonasson T, Ohlin H, Lindgren A, Hultberg B. Vitamin supplementation normalizes total plasma homocysteine concentration but not plasma homocysteine redox status in patients with acute coronary syndromes and hyperhomocysteinemia. <i>Clin Chem Lab Med</i>. 2002 Jun; 40 (6): 554-558. PMID: 12211647.</p>	<p>About homocysteine.</p>
<p>Assanelli D, Bonanome A, Pezzini A, Albertini F, Maccalli P, Grassi M, Archetti S, Negrini R, Visioli F. Folic acid and vitamin E supplementation effects on homocysteinemia, endothelial function and plasma antioxidant capacity in young myocardial-infarction patients. <i>Pharmacol Res</i>. 2004 Jan; 49 (1): 79-84. Erratum in: <i>Pharmacol Res</i>. 2004 May; 49 (5): 501. Maccalli, Pietro [corrected to Maccalli, Paola]; Negrini, Roberto [corrected to Negrini, Riccardo]. PMID: 14597156.</p>	<p>About homocysteine</p>

<p>Chambers JC, Obeid OA, Refsum H, Ueland P, Hackett D, Hooper J, Turner RM, Thompson SG, Kooner JS. Plasma homocysteine concentrations and risk of coronary heart disease in UK Indian Asian and European men. <i>Lancet</i>. 2000 Feb 12; 355 (9203): 523-527. PMID: 10683001.</p>	<p>It does not address CVD or stroke risk.</p>
<p>Constans J, Blann AD, Resplandy F, Parrot F, Renard M, Seigneur M, Guérin V, Boisseau M, Conri C. Three months supplementation of hyperhomocysteinaemic patients with folic acid and vitamin B6 improves biological markers of endothelial dysfunction. <i>Br J Haematol</i>. 1999 Dec; 107 (4): 776-778. PMID: 10606884.</p>	<p>Article prior June 2004.</p>
<p>Deicher R, Vierhapper H. Homocysteine: A risk factor for cardiovascular disease in subclinical hypothyroidism? <i>Thyroid</i>. 2002 Aug; 12 (8): 733-736. PMID: 12225643.</p>	<p>About homocysteine and hypothyroidism.</p>
<p>Galan P, de Bree A, Mennen L, Potier de Courcy G, Preziozi P, Bertrais S, Castetbon K, Hercberg S. Background and rationale of the SU.FOL.OM3 study: Double-blind randomized placebo-controlled secondary prevention trial to test the impact of supplementation with folate, vitamin B₆ and B₁₂ and/or omega-3 fatty acids on the prevention of recurrent ischemic events in subjects with atherosclerosis in the coronary or cerebral arteries. <i>J Nutr Health Aging</i>. 2003; 7 (6): 428-435. PMID: 14625623.</p>	<p>Background and rationale of the SU FOL OM3 study.</p>
<p>Guo H, Lee JD, Ueda T, Cheng J, Shan J, Wang J. Hyperhomocysteinaemia and folic acid supplementation in patients with high risk of coronary artery disease. <i>Indian J Med Res</i>. 2004 Jan; 119 (1): 33-37. PMID: 14997992.</p>	<p>Article prior June 2004.</p>
<p>Hernández-Díaz S, Martínez-Losa E, Fernández-Jarne E, Serrano-Martínez M, Martínez-González MA. Dietary folate and the risk of non-fatal myocardial infarction. <i>Epidemiology</i>. 2002 Nov; 13 (6): 700-706. PMID: 12410012.</p>	<p>Article prior June 2004.</p>
<p>Lee BJ, Huang MC, Chung LJ, Cheng CH, Lin KL, Su KH, Huang YC. Folic acid and vitamin B₁₂ are more effective than vitamin B₆ in lowering fasting plasma homocysteine concentration in patients with coronary artery disease. <i>Eur J Clin Nutr</i>. 2004 Mar; 58 (3): 481-487. PMID: 14985687.</p>	<p>It does not address CVD or stroke risk.</p>
<p>Lee BJ, Lin PT, Liaw YP, Chang SJ, Cheng CH, Huang YC. Homocysteine and risk of coronary artery disease: Folate is the important determinant of plasma homocysteine concentration. <i>Nutrition</i>. 2003 Jul-Aug; 19 (7-8): 577- 583. PMID: 12831941.</p>	<p>Article prior June 2004.</p>

<p>Lobo A, Naso A, Arheart K, Kruger WD, Abou-Ghazala T, Alsous F, Nahlawi M, Gupta A, Moustapha A, van Lente F, Jacobsen DW, Robinson K. Reduction of homocysteine levels in coronary artery disease by low-dose folic acid combined with vitamins B₆ and B₁₂. <i>Am J Cardiol.</i> 1999 Mar 15; 83 (6): 821-825. PMID: 10190392.</p>	<p>About homocysteine.</p>
<p>Mark L, Erdei F, Markizay J, K Effect of treatment with folic acid and vitamin B₆ on lipid and homocysteine concentrations in patients with coronary artery disease. <i>Nutrition.</i> 2002 May; 18 (5): 428-429. No abstract available. PMID: 11985950.</p>	<p>Article prior June 2004.</p>
<p>McCully KS Homocysteine, vitamins and prevention of vascular disease. <i>Mil Med.</i> 2004 Apr; 169 (4): 325-329. PMID: 15132238</p>	<p>About homocysteine.</p>
<p>Neal B, MacMahon S, Ohkubo T, Tonkin A, Wilcken D Dose-dependent effects of folic acid on plasma homocysteine in a randomized trial conducted among 723 individuals with coronary heart disease. PACIFIC Study Group. <i>Eur Heart J.</i> 2002 Oct; 23 (19): 1, 509-1, 515. PMID: 12395803.</p>	<p>About homocysteine.</p>
<p>Potena L, Grigioni F, Magnani G, Sorbello S, Sassi S, Poci MG, Carigi S, Bacchi-Reggiani L, Leone O, Magelli C, Branzi A. Folate supplementation after heart transplantation: Effects on homocysteine plasma levels and allograft vascular disease. <i>Clin Nutr.</i> 2002 Jun; 21 (3): 245-248. Erratum in: <i>Clin Nutr.</i> 2003 Feb; 22 (1): 107. Magnai G [corrected to Magnani G]. PMID: 12127934.</p>	<p>About homocysteine</p>
<p>Stanger O. The potential role of homocysteine in percutaneous coronary interventions (PCI): Review of current evidence and plausibility of action. <i>Cell Mol Biol (Noisy-le-grand).</i> 2004 Dec; 50 (8): 953-988. Review. PMID: 15704259.</p>	<p>Not a systematic review.</p>
<p>Stanger O, Semmelrock HJ, Wonisch W, Bös U, Pabst E, Wascher TC. Effects of folate treatment and homocysteine lowering on resistance vessel reactivity in atherosclerotic subjects. <i>J Pharmacol Exp Ther.</i> 2002 Oct; 303 (1): 158-162. PMID: 12235246.</p>	<p>It does not address CVD or stroke risk</p>
<p>Thambyrajah J, Landray MJ, Jones HJ, McGlynn FJ, Wheeler DC, Townend JN. A randomized double-blind placebo-controlled trial of the effect of homocysteine-lowering therapy with folic acid on endothelial function in patients with coronary artery disease. <i>J Am Coll Cardiol.</i> 2001 Jun 1; 37 (7): 1, 858-1, 863. PMID: 11401123.</p>	<p>Article prior June 2004.</p>

<p>Tice JA, Ross E, Coxson PG, Rosenberg I, Weinstein MC, Hunink MG, Goldman PA, Williams L, Goldman L. <u>Cost-effectiveness of vitamin therapy to lower plasma homocysteine levels for the prevention of coronary heart disease: Effect of grain fortification and beyond.</u> <i>JAMA</i>. 2001 Aug 22-29; 286 (8): 936-943. PMID: 11509058.</p>	<p>Model to predict risk of CVD.</p>
<p>Title LM, Cummings PM, Giddens K, Genest JJ Jr, Nassar BA. <u>Effect of folic acid and antioxidant vitamins on endothelial dysfunction in patients with coronary artery disease.</u> <i>J Am Coll Cardiol</i>. 2000 Sep; 36 (3): 758-765. PMID: 10987596.</p>	<p>Article prior June 2004.</p>
<p>Wald DS, Bishop L, Wald NJ, Law M, Hennessy E, Weir D, McPartlin J, Scott J. <u>Randomized trial of folic acid supplementation and serum homocysteine levels.</u> <i>Arch Intern Med</i>. 2001 Mar 12; 161 (5): 695-700. PMID: 11231701.</p>	<p>It does not address CVD or stroke risk</p>
<p>Weiss N, Hilge R, Hoffmann U, Vasa. <u>Mild hyperhomocysteinemia: Risk factor or just risk predictor for cardiovascular diseases?</u> 2004 Nov; 33 (4): 191-203. Review. PMID: 15623193.</p>	<p>Not a systematic review.</p>
<p>Woo KS, Chook P, Chan LL, Cheung AS, Fung WH, Qiao M, Lolin YI, Thomas GN, Sanderson JE, Metreweli C, Celermajer DS. <u>Long-term improvement in homocysteine levels and arterial endothelial function after one-year folic acid supplementation.</u> <i>Am J Med</i>. 2002 May; 112 (7): 535-539. PMID: 12015244.</p>	<p>Article prior June 2004.</p>
<p>Woo KS, Chook P, Lolin YI, Sanderson JE, Metreweli C, Celermajer DS. <u>Folic acid improves arterial endothelial function in adults with hyperhomocystinemia.</u> <i>J Am Coll Cardiol</i>. 1999 Dec; 34 (7): 2, 002-2, 006. PMID: 10588216.</p>	<p>Article prior June 2004.</p>

Excluded Articles	Reason for Exclusion
<p>Drogan D, Klipstein-Grobusch K, Dierkes J, Weikert C, Boeing H. <u>Dietary intake of folate equivalents and risk of myocardial infarction in the European Prospective Investigation into Cancer and Nutrition (EPIC) Potsdam study.</u> <i>Public Health Nutr</i>. 2006 Jun; 9 (4): 465-471. PMID: 16870018 International.</p>	<p>It does not answer the question.</p>
<p>Hodis HN, Mack WJ, Dustin L, Mahrer PR, Azen SP, Detrano R, Selhub J, Alaupovic P, Liu CR, Liu CH, Hwang J, Wilcox AG, Selzer RH; BVAIT Research Group. <u>High-dose B vitamin supplementation and progression of subclinical atherosclerosis: a randomized controlled trial.</u> <i>Stroke</i>. 2009 Mar; 40 (3): 730-736. Epub 2008 Dec 31. PMID: 19118243.</p>	<p>It does not answer the question.</p>

<p>Liem A, Reynierse-Buitenwerf GH, Zwinderman AH, Jukema JW, van Veldhuisen DJ. Secondary prevention with folic acid: Effects on clinical outcomes. <i>J Am Coll Cardiol.</i> 2003 Jun 18; 41 (12): 2, 105-2, 113. PMID: 12821232.</p>	<p>Articles included in the Bazzano meta-analysis article.</p>
<p>Liem AH, van Boven AJ, Veeger NJ, Withagen AJ, Robles de Medina RM, Tijssen JG, van Veldhuisen DJ; Folic Acid on Risk Diminishment After Acute Myocardial Infarction Study Group. Efficacy of folic acid when added to statin therapy in patients with hypercholesterolemia following acute myocardial infarction: a randomised pilot trial. <i>Int J Cardiol.</i> 2004 Feb; 93 (2-3): 175-179. PMID: 14975544.</p>	<p>Articles included in the Bazzano meta-analysis article.</p>
<p>Lonn E, Yusuf S, Arnold MJ, Sheridan P, Pogue J, Micks M, McQueen MJ, Probstfield J, Fodor G, Held C, Genest J Jr; Heart Outcomes Prevention Evaluation (HOPE) 2 Investigators. Homocysteine lowering with folic acid and B vitamins in vascular disease. <i>N Engl J Med.</i> 2006 Apr 13; 354 (15): 1, 567-1, 577. Epub 2006 Mar 12. Erratum in: <i>N Engl J Med.</i> 2006 Aug 17; 355 (7): 746. PMID: 16531613.</p>	<p>Articles included in the Bazzano meta-analysis article.</p>
<p>Shirodaria C, Antoniades C, Lee J, Jackson CE, Robson MD, Francis JM, Moat SJ, Ratnatunga C, Pillai R, Refsum H, Neubauer S, Channon KM. Global improvement of vascular function and redox state with low-dose folic acid: Implications for folate therapy in patients with coronary artery disease. <i>Circulation.</i> 2007 May 1;115 (17): 2, 262-2, 270. Epub 2007 Apr 9. PMID: 17420345.</p>	<p>It does not answer the question.</p>
<p>Vrentzos GE, Papadakis JA, Malliaraki N, Zacharis EA, Mazokopakis E, Margioris A, Ganotakis ES, Kafatos A. Diet, serum homocysteine levels and ischaemic heart disease in a Mediterranean population. <i>Br J Nutr.</i> 2004 Jun; 91 (6): 1, 013-1, 019. PMID: 15182405 International.</p>	<p>It does not answer the question.</p>